The Association Between Prenatal Stress And Externalizing Symptoms In Childhood: Evidence From The Avon Longitudinal Study Of Parents And Children

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ABSTRACT

Background: It has been suggested that prenatal maternal stress may increase risk of childhood externalizing disorders, yet no large cohort study has investigated this association across a large range of acute stressors. Our objective was to estimate the association between prenatal stressful events and risk of offspring conduct disorder and hyperactivity.

Methods: We used data from 10,184 mother-offspring pairs from the UK-based Avon Longitudinal Study of Parents and Children. Mothers self-reported 42 prenatal stressful life events at 18 weeks gestation. Symptoms of conduct disorder and hyperactivity were measured at age 6, 9, 11, 13, and 16 by the Strengths and Difficulties Questionnaire. The primary outcome was membership in high-symptom trajectories of (1) conduct disorder and (2) hyperactivity throughout childhood, identified using latent class growth modeling. Multinomial logistic regression models estimated the association between prenatal stress and both conduct disorder and hyperactivity, after adjusting for sex, parental education, low birth weight, pre-term birth, parental social class, maternal smoking and drinking, maternal mental health, offspring stressful life events, and offspring depressive and anxious symptoms.

Results: Those exposed to the highest quartile of prenatal stress were more likely to belong to the high symptom trajectory for hyperactivity ($B = 0.46$, $p<.05$) and conduct disorder ($B = 0.88$, $p<.01$), respectively. Prenatal stress further demonstrated a positive, dose response relationship with symptoms of externalizing disorders at independent time points.

Conclusions: The findings suggest that prenatal stressful events may be an independent risk factor for offspring externalizing symptoms, regardless of maternal mental health and offspring internalizing.

INTRODUCTION

The developmental programming hypothesis suggests that a fetus adapts to maternal cues about the external environment during critical periods of development (1; 2). The small adaptations undergone *in utero* can have long-term consequences on child behavior and health, and may predispose the individual to later adverse health outcomes, including mental and behavioral disorders (3). For example, low birth weight, a common consequence of prenatal adversity, is correlated with severity of attention deficient hyperactivity disorder (ADHD) and behavioral problems (4–6).

More specifically, it is posited that prenatal stress may permanently alter the hypothalamic-pituitary-adrenal (HPA) axis of fetus' stress response, predisposing the offspring to maladaptive stress responses. Deregulation of cortisol, cytokines, and serotonin functioning are suggested drivers of the abnormal HPA response, as demonstrated in both rodents and primates (7–9). In nonhuman primates, offspring of stressed mothers show higher cortisol levels at both baseline and in response to stressful events (10). Similarly, antenatally stressed rodents have longer stress responses, and show many behavioral changes analogous to externalizing disorders in humans, such as declined attention and impaired learning or memory (11).

In humans, maternal prenatal depression and anxiety have been associated with offspring externalizing problems (12–14). Childhood externalizing disorders are characterized by aggressive or antisocial behaviour, high activity levels, and difficulty inhibiting behaviour. Externalizing disorders are associated with considerable negative outcomes in adolescence and adulthood, including school failure, substance use/abuse, and criminal activity (15; 16).

Despite the established theoretical basis of disease and association with future consequences, there remains a dearth of evidence elucidating the clinical parameters of adverse

prenatal stress and its consequences on externalizing disorders in the offspring. One current limitation in the literature is the complexity of assessing maternal stress. To date, maternal anxiety, depression and perceived general stress are the main markers of maternal adversity (12–14; 17–20). For example, results from one prospective study using the Avon Longitudinal Study of Parents and Children (ALSPAC) cohort suggested that high maternal anxiety during pregnancy was associated with a trajectory of persistent conduct problems throughout childhood (17). However, this study did not assess maternal exposure to specific stressors. Maternal anxiety and general perceptions of stress are a function of subjective coping strategies and social support, and they are vulnerable to overlapping conceptualizations (21). Stressful life events are a more objective marker of maternal adversity. Exposure to specific prenatal stressful events has previously been shown to correlate with symptoms of ADHD in two retrospective case-control studies, and two prospective registry studies found an association between the death of a loved one during pregnancy and offspring ADHD (22–25). In a third prospective study, Robinson et al. used a list of 10 stressful events to assess risk of externalizing and internalizing disorders, but did not account for the severity of each stressful event (26). Finally, Ronald et al. reported that mothers' experience of acute stressful life events was associated with offspring symptoms of ADHD at age 2 (27). There remains a need for prospective studies examining more comprehensive measures of acute prenatal stressors on externalizing outcomes later in childhood/adolescence.

A second limitation is the failure to assess the association in the context of parental history of depression, maternal depression, and childhood internalizing disorders. Maternal depression and childhood internalizing problems strongly correlate with prenatal stress, abnormal HPA functioning, and externalizing disorders, making them strong confounders of the

association (28–31), yet few studies have appropriately adjusted for these factors. Li et al. controlled for psychiatric hospital admissions and Class et al. controlled for severe mental illnesses such as suicide attempts, schizophrenia and bipolar disorder, but were unable to adjust for common internalizing symptoms (23; 24).

The objective of the present study was to investigate the association between stressful events during pregnancy and offspring externalizing disorder symptoms, controlling for maternal and paternal history of depression, maternal depression during childhood, and childhood internalizing symptoms. A recent review concluded there are a disproportionate number of studies investigating ADHD as an outcome, at the expense of other disorders, such as conduct disorders (32). Conversely, Barker and Maughan (2009) used ALSPAC data to examine relationships between maternal anxiety and trajectories of conduct disorder, but not hyperactivity (17). Consequently, externalizing disorders are assessed in the present study by symptoms of both hyperactivity and conduct disorders so as to compare and contrast the association within the study and in the context of existing literature. The correlates of externalizing behaviour have been shown to differ based on the specific developmental profile of symptoms (e.g., early vs. late onset, persistent vs. childhood-limited)(33). For example, early-onset, life-course persistent trajectories of externalizing behaviour are more strongly associated with early childhood risk factors such as poverty, maltreatment, and family conflict than are adolescent-onset or childhood-limited trajectories (34). As a result, many researchers have argued for the examination of developmental trajectories of externalizing symptoms over time (35; 36). In this study, we employ latent class growth modeling (LCGM) to identify latent trajectories of externalizing symptoms over time.

We hypothesized that children whose mothers reported higher levels of prenatal stressful events would be at a higher risk for trajectories characterized by persistently high symptoms of externalizing disorders.

METHODS AND MATERIALS

Sample

We used the Avon Longitudinal Study of Parents and Children, a trans-generational, prospective birth cohort based in southwest England. It comprises 14062 live births from women expected to deliver between April 1991 and December 1992. All pregnant women were eligible to participate, and were recruited through media, community centres and maternity clinics. Please note that the study website contains details of all the data that is available through a fully searchable data dictionary (http://www.bris.ac.uk/alspac/researchers/data-access/data-dictionary). ALSPAC is broadly nationally representative, with a slight oversampling of wealthy, Caucasian families as is typical of the Avon region (37).

All individuals with outcome data were included in the analyses. Sample size varied by year, with 10,184 mothers reporting on conduct disorder in their offspring at one time point or more, and 10,174 mothers reporting on hyperactivity in their offspring at one time point or more (Supplemental Figure 1). Attrition in ALSPAC resulted in a sample of 5657 individuals with outcome data at age sixteen. Notably, attrition by age 16 was associated with both maternal prenatal stress and offspring conduct and hyperactivity symptoms at age 7 (Supplemental Table 1; see Discussion for further comment).

All participants provided informed consent; ethical approval for the study was obtained from the ALSPAC Ethics and Law Committee and the Local Research Ethics Committees and by the Ottawa Health Science Network Research Ethics Board.

Exposure

Stressful life events in early pregnancy were assessed at eighteen weeks gestation through a postal questionnaire. Participants were asked if any of 42 stressful events had occurred since

pregnancy and to rate their impact ('0' – did not occur, '1'- yes but did not affect me to '4'-yes, and affected me greatly; Supplemental Table 2). Total stressful event score was calculated by the sum of an individual's answers (possible range 0-168), and then the score was coded into quartiles to facilitate interpretation. Quartile thresholds were at 3, 5 and 12.

Outcome

Conduct problems and hyperactivity were assessed using the Strengths and Difficulties Questionnaire (SDQ), a well-validated, 25-item screening questionnaire used to assess symptoms of internalizing and externalizing problems in childhood (26, 27). Parent-reported SDQ scores are widely used and show good predictive validity, converging with DSM-IV criteria (40). For each question, caregivers identified whether the listed behavior was 'Not True', 'Somewhat True', or 'Certainly True' of their child, yielding possible scores from 0-10 for each of hyperactivity (5 items, e.g. 'restless, overactive, cannot stay still for long') and conduct disorder (5 items, e.g. 'often has temper tantrums or hot tempers'). The SDQ was administered five times: at ages 7, 9, 11, 13, and 16 years.

Covariates

The analyses were adjusted for demographic and physiological measures associated with symptoms of hyperactivity and conduct disorder. These variables were included as covariates in the adjusted regression models, and include sex, maternal education (above/below A level), low birth weight (<2500g), pre-term birth (<37 weeks gestation), social class (SES) as measured by the highest Office of National Statistics occupation classification between parents, teenage pregnancy, ethnicity (white/non-white), smoking (none/any in first 18 weeks), and alcohol (<1 drink/week in first three months), as well as maternal psychiatric measures (history or current depression, prenatal depression, prenatal anxiety, postpartum depression, stressful life events at 8

months), paternal history of depression, and offspring stressful life events during childhood. Birthweight and gestational age were obtained from hospital records and dichotomized based on widely-used cutoffs (41). History of depression (yes/no) was self-reported at 12 weeks gestation. Prenatal and post partum depression were assessed from the mean score of the Edinburgh Postnatal Depression Scale (EPDS) at 18 weeks/32 weeks and 8weeks/8 months respectively. Scores were subsequently dichotomized using the recommended cut-off score for major depression for the EPDS (12 out of a possible 30) (42; 43). Prenatal anxiety was obtained using the Crown Crisp anxiety subscale with scores dichotomized at the 85th percentile, as suggested in previous studies using this measure (44). Stressful life events at 8 months postpartum were assessed using a questionnaire inventory of 42 events (similar to the prenatal stress inventory, with stressors specific to pregnancy excluded). Number of stressful life events during childhood were reported by caregivers at 1, 2, 3, 4, 5, and 6 years of age using an inventory of 15 possible events.

Finally, symptoms of depression and anxiety in the child at each corresponding outcome time point, as measured by the SDQ emotional symptoms subscale (5 items, e.g. 'often unhappy, downhearted, or tearful'), were included as covariates in the model.

Statistical Analysis

Latent class growth modeling (LCGM) using a censored normal distribution was used to identify trajectories of conduct disorder and hyperactivity symptoms independently over time. LCGM is a semi-parametric, group-based approach, which produces homogeneous latent trajectories from longitudinal data (45). Unlike parametric approaches, LCGM does not assume a continuous distribution of trajectories within the population, which makes it well suited for studying phenomena where a) distribution of symptoms are highly skewed, as is the case for externalizing

disorders, and b) trajectories are assumed to be categorical (as trajectories of externalizing behaviour have been hypothesized to be (36)). The PROC TRAJ application was used in SAS version 9.4 because it allows for irregular spacing of measurements, as is the case here. A censored normal distribution was used to overcome the problem of clustering at the extremes of a psychometric scale (36). The appropriate model was selected based on a combination of criteria: improving Bayesian Information Criterion (BIC), maximizing average posterior probabilities for each group (>75%), and maintaining group size and interpretability. Multinomial logistic regression was subsequently used to calculated relative risk ratios and 95% confidence intervals for membership in trajectory groups by quartiles of prenatal stress.

Additionally, we conducted a supplementary analysis using latent growth curve modeling (LGM). LGM analysis is used to describe an average developmental trajectory for the population (e.g., linear, with a mean intercept and slope), but parameters (i.e. slope and intercept) are allowed to vary across individuals. Thus, children may start with higher or lower than average externalizing symptoms, and these symptoms may vary at different rates (or in different directions). Covariates (in this case, maternal prenatal stress) can then be used to predict changes in the intercept and slope of the trajectory. Growth curves were fitted separately for child hyperactivity and conduct disorder symptoms from age 7 – 16, using an SEM approach in Stata version 12.

Finally, multivariate regressions were performed for SDQ conduct disorder and hyperactivity scores independently at each time point. Regression coefficients and p-values are reported for externalizing disorders across quartiles of prenatally stressed mothers, as well as for continuous maternal stress scores. Given externalizing disorders vary by sex, an interaction between sex and prenatal stress was investigated (46).

To account for missing data, exposure and all covariates were imputed by fully conditional specification using chained equations. The five-iteration multiple imputation model included all variables used in the final prediction models (outcome variables were used in the imputation model but were not themselves imputed). The imputation model employed logistic regression for categorical covariates and linear regression for continuous covariates.

All analyses (excluding the trajectory modeling) were conducted using Stata version 12 (47).

RESULTS

Baseline measures

Sample mothers were predominantly well educated, of a high socioeconomic status, and non-smoking (Table 1). Stressful event burden was positively associated with preterm birth, low birth weight, teenage maternal age at birth, maternal substance use, low maternal education, non-white child ethnicity, and numerous measures of poor parental psychological health.

Association between prenatal stress and externalizing disorder trajectories

For both conduct disorder and hyperactivity symptoms, a four-group model was chosen based on fit statistics, posterior probabilities, interpretability, and meaningful group sizes (Supplemental Table 3). Symptom trajectories are represented graphically in Figure 1. For both hyperactivity and conduct disorder, groups represented youth exhibiting no to very low symptoms over time ("no symptoms"), low stable symptoms ("low symptoms"), moderate stable symptoms ("moderate symptoms"), and consistently high symptoms over time ("high symptoms").

The multinomial logistic regressions of prenatal stress on group membership demonstrate strong evidence that increasing levels of stress predict higher odds of belonging to trajectories characterized by higher symptoms for both conduct disorder (Table 2) and hyperactivity (Table 3). The association persisted for both conduct disorder and hyperactivity in the adjusted model.

As a secondary analysis, we investigated growth curves for symptoms of conduct disorder and hyperactivity using LGM. For conduct disorder, a linear model with random intercept and slope proved a better fit to the data than the intercept only model (i.e., a model of stable symptoms over time; Chi square for the likelihood ratio test: $\chi^2 = 827.36$, $p < .0001$). The estimated growth curve for the population had a mean intercept of 1.52 (which differed significantly from zero, $p<.001$) and a mean slope of -0.10 ($p<.001$). When all covariates were

included in the model, maternal stress (continuous, 168 point scale) predicted an increase in the intercept (0.01, p<.001) and was not associated with slope (0.001, p=.419).

For hyperactivity symptoms, the slope and intercept model again showed better fit than the intercept only model ($\chi^2 = 889.82$, $p < .0001$). The mean intercept for the growth curve was 3.28 (p<.001), and the mean slope was -0.14 (p<.001). After adjusting for covariates, increasing maternal stress was associated with an increase in the intercept (0.02, p<.001) and did not significantly predict slope (-0.00, p=.823).

Association between prenatal stressful events and offspring externalizing disorders at individual ages

Prenatal maternal stressful events were associated with both offspring symptoms of conduct disorder and hyperactivity at specific ages (Tables 4 and 5). For conduct disorder, there was a dose response relationship with increasing odds of conduct disorder symptoms for each additional quartile of stressful life events at all time points. In the adjusted model, the association was significant only for the highest quartile of stressful events (with the exception of ages 7 and 16 years). Notably, the magnitude of the association did not decrease over time for the children of mothers in the highest quartile of stressful events. For hyperactivity, a similar dose response with increasing prenatal maternal stressful events was observed. The evidence for an association was strongest at 7 years, and remained significant at the highest level of prenatal stress until age 16. Results from liner regressions supported these results, with a one-unit increase in mothers' prenatal stress scores predicting increased conduct symptoms at all ages, and increased hyperactivity symptoms at 7, 13, and 16 years.

In all cases, no evidence of an interaction with sex was found (results not shown).

DISCUSSION

This sixteen-year prospective study of more than 10,000 mother/child pairs demonstrated an association between maternal stressful life events during pregnancy and subsequent risk of conduct disorder and hyperactivity symptoms in the offspring. Prenatal stress increased the risk for conduct disorder and hyperactivity symptoms throughout childhood in those with high maternal stress (i.e., top quartile), persisting until age 16. Moreover, the risks persisted after adjusting for post-natal stress and childhood internalizing symptoms, suggesting prenatal stress was specifically associated with externalizing disorders.

Latent trajectory analysis suggested four parallel trajectories of stable symptoms over time, with the majority of children exhibiting stable low symptoms across childhood and adolescence. This was somewhat counter to expectations – previous studies examining externalizing behaviour over time have found evidence for developmental classes characterized by childhood limited (i.e., high in childhood, decreasing in adolescence) and adolescent onset (i.e., low in childhood, increasing in adolescence) symptoms(33; 36). One possibility is that these changes in symptom level may occur outside the age range represented by the present data. Given that trajectories were observed to be roughly parallel, we conducted a secondary analysis using growth curve modeling, fitting a single linear growth curve to the data. Results were congruent with the above – overall, symptoms of externalizing problems were stable over time (decreasing slightly), with a relatively low mean initial level. Maternal stress predicted a higher level of both conduct and hyperactivity symptoms at age 7, but did not affect the rate of change in symptoms over time.

Taken together, these results support the existing literature: prenatal maternal depression and anxiety have been correlated with increased risk of many childhood externalizing problems,

including hyperactivity and conduct disorders (7; 17; 19; 20; 27). One study demonstrated a similar dose response between number of stressful life events and any externalizing disorder (26); however, our study is the first to use a broader range of stressful events and assess more specific externalizing disorders—both hyperactivity and conduct disorder—while controlling for maternal mental health and childhood internalizing. The study further extends existing research on prenatal stress and externalizing disorders by showing an analogous association that persists into adolescence (20). Lastly, we did not find any sex differences, contrary to one previous report on prenatal anxiety (48), but consistent with another (17), as well as with two studies on prenatal stressful events (26; 27).

Our results support the fetal development hypothesis, which posits that early-life environmental factors have long-term consequences on ill health. Importantly, the association persisted after adjusting for internalizing disorder symptoms, suggesting that a secondary mechanism independent of internalizing disorders may contribute to the development of externalizing disorders. One possibility is that elevated maternal cortisol (as a response to environmental stressors) results in elevated levels of testosterone in the uterine environment. Maternal cortisol is correlated with both fetal cortisol and fetal testosterone levels (49; 50). Testosterone subsequently can cause permanent changes in neurodevelopment and delayed biological maturation (51). Two small studies of children demonstrated an association between testosterone and subsequent behavioral outcomes in the offspring; the first between amniotic testosterone and reduced sociability (i.e. less eye contact, less empathy) and the second between serum testosterone, aggression and inattention (52–54). Together, evidence suggests testosterone may specifically be associated with externalizing disorder profiles (11).

Alternatively, maternal prenatal stress may have an effect on offspring dopamine signalling. Offspring of prenatally stressed mothers have been shown to exhibit a higher ratio of dopamine receptors and dopamine than controls (55). Independently, a second study demonstrated that dopamine receptor availability is associated with inhibition failure of adolescents with ADHD. The latter study was conducted in only a small sample, but is consistent with additional studies of abnormal function of brain activity in ADHD children (11).

The results presented in this study should be interpreted in the context of some limitations. We do not include genetic information in our analysis, but by adjusting for maternal and paternal history of depression, we provide strong evidence that there is an independent effect of prenatal stress in addition to possible genetic confounders. This is consistent with current literature whereby the same correlation persists after controlling for maternal postpartum adversity and paternal stress (7; 19; 56), as well as in children of in vitro fertilizations with genetically unrelated mothers (57). Secondly, information on exposure and outcome were both obtained by maternal report. Thus, the possibility of reporter bias cannot be ruled out. However, parent-reported SDQ scores are well-validated and widely used to measure child internalizing and externalizing problems. Thirdly, attrition over the 16-year follow-up period was observed, and was associated with both exposure and both outcome measures at age 7. However, such attrition would bias study results in a conservative direction, suggesting the true effect may be stronger than what is reported in this study. Finally, our study uses only one time point for stressful life events during pregnancy. Consequences on the fetus have shown to vary with time-varying exposures (18, 42), and our study was unable to capture possible time-dependent effects of prenatal stressful life events. Given the strong correlation found in this study, future research should investigate exposure across time.

Despite these limitations, this study has numerous strengths. This study used a specific measure of maternal stressful events rather than symptoms of anxiety and depression. By using more than forty stressor prompts and taking into account severity of the event, we provide a comprehensive measure of maternal stress that can appropriately disentangle the effects of stress from the mother's coping ability. Moreover, by addressing objective stressful events rather than anxiety or depression, we include subclinical levels of stress and so, allow for a better representation of the dose-response relationship. By including multiple assessments of stressful life events throughout the offspring's childhood as covariates, we can more accurately isolate stress during the prenatal period. Finally, the large sample size allows for adjustment of multiple confounders previously excluded in the existing literature. Our study provides comprehensive evidence that stressful events are associated with offspring externalizing disorders, independent of maternal mental health and childhood comorbid depression/anxiety.

Conclusion

These results emphasize the potential impact of maternal stress during pregnancy on offspring, in a dose-response manner that is independent of maternal mental health and offspring internalizing symptoms. Previously, the attributable risk of prenatal stress on childhood behavioral problems has been estimated as high as 10-15% (7). Therefore, the implications of this research have potential implications for hyperactivity and conduct disorder as well as other behavioural problems. Although many stressful life events are unpredictable, recognizing and validating the consequences of prenatal stress on externalizing disorders is a crucial first step to developing interventions for highly stressed pregnant women. Past research demonstrates that mother-child attachment moderates the association between prenatal stress and offspring neurodevelopment

(59), suggesting the effects of prenatal stress may be mitigated by early interventions aimed at increasing attachment.

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Table 1: Sample characteristics of the study sample according to quartiles of prenatal stress

	Study Sample	**Prenatal Stress by Quartile**					**Missing Data**
Covariates	**N=7699**	**1st**	**2nd**	**3rd**	**4th**	**P value***	
Sex (Male)	51.64	52.31	51.09	53.26	49.59	0.140	0
Preterm Birth	5.17	4.08	4.62	6.20	5.76	0.011	0
Low Birth weight	4.38	3.22	4.11	4.79	5.44	0.013	1.17
Teen Pregnancy	2.01	1.20	1.45	1.99	3.73	<0.001	0
Maternal smoking, last 2 weeks	15.20	11.47	12.76	15.55	22.26	<0.001	0.17
Maternal alcohol misuse, first trimester	15.52	13.70	1412	16.64	18.03	0.001	0.35
Low maternal Education (no A level)	40.84	36.20	40.29	44.05	42.30	<0.001	1.90
Non-white Child Ethnicity	3.64	2.71	3.01	3.48	5.81	<0.001	3.21
Low SES (Non-professional)	3.92	3.96	3.72	3.03	3.86	0.884	7.78
Mother ever depressed	7.58	3.71	4.71	8.26	15.05	<0.001	7.47
Maternal prenatal depression	10.76	3.30	5.99	11.50	24.67	<0.001	0.01
Maternal prenatal anxiety	12.13	4.03	7.27	12.70	27.14	<0.001	0.12
Maternal postnatal depression	7.34	2.50	5.14	7.77	15.14	<0.001	1.40
Partner ever depressed	5.55	3.16	3.54	6.54	10.25	<0.001	27.67
	Mean (SD)					**P value***	
Maternal postnatal stress	9.52 (7.82)	5.95 (5.47)	7.91 (6.42)	10.3 (7.52)	14.79 (9.93)	< 0.001	3.91
Child SLES age 1	0.93 (1.06)	0.73 (0.98)	0.85 (1.01)	1.05 (1.12)	1.28 (1.28)	< 0.001	3.38
Child SLES age 2	1.35 (1.30)	1.12 (1.18)	1.27 (1.20)	1.46 (1.31)	1.69 (1.41)	< 0.001	5.59
Child SLEs age 3	1.62 (1.26)	1.39 (1.13)	1.56 (1.21)	1.70 (1.28)	1.95 (1.44)	< 0.001	5.36
Child SLES age 4	2.32 (1.38)	2.09 (1.21)	2.26 (1.32)	2.38 (1.44)	2.77 (1.60)	< 0.001	5.64
Child SLES age 5	1.42 (1.26)	1.20 (1.11)	1.33 (1.17)	1.49 (1.29)	1.75 (1.51)	< 0.001	8.10
Child SLES age 6	1.42 (1.46)	1.12 (1.20)	1.31 (1.34)	1.52 (1.50)	1.75 (1.71)	< 0.001	0.00

**P-values correspond to Pearson's chi squared test for categorical covariates and to the omnibus F-test for ANOVA for continuous covariates*

Table 2. Results of multinomial logistic regression predicting conduct disorder trajectory membership (reference trajectory = no symptoms) from mothers' prenatal stressful life events.

	Low symptoms		Moderate Symptoms		High Symptoms	
Crude model	B	p value	B	p value	B	p value
2nd quartile stress	**0.14**	**<.05**	**0.40**	**<.001**	0.41	.11
3rd quartile stress	**0.28**	**<.001**	**0.59**	**<.001**	**0.78**	**<.01**
4th quartile stress	**0.44**	**<.001**	**1.03**	**<.001**	**1.51**	**<.001**
Stress (continuous)	**0.02**	**<.001**	**0.05**	**<.001**	**0.06**	**<.001**
Adjusted model *						
2nd quartile stress	0.11	.124	**0.32**	**<.01**	0.34	.241
3rd quartile stress	**0.19**	**<.05**	**0.34**	**<.01**	0.47	.104
4th quartile stress	**0.27**	**<.01**	**0.46**	**<.001**	**0.88**	**<.01**
Stress (continuous)	**0.01**	**<.01**	**0.02**	**<.01**	**0.03**	**<.05**

* Adjusted for sex, maternal education, low birth weight, pre-term birth, ethnicity, SES, teenage pregnancy, prenatal smoking and alcohol use, maternal and paternal history of depression, maternal prenatal depression, maternal prenatal anxiety, maternal postpartum depression, maternal stressful life events at 8 months, offspring stressful life events (at ages 1, 2, 3, 4, 5, and 6 years), and offspring symptoms of depression/anxiety at 81 months.

Table 3. Results of multinomial logistic regression predicting hyperactivity trajectory membership (reference trajectory = no symptoms) from mothers' prenatal stressful life events.

	Low symptoms		Moderate Symptoms		High Symptoms	
Crude model	B	p value	B	p value	B	p value
2nd quartile stress	0.12	.093	0.24	<.01	0.28	.117
3rd quartile stress	**0.23**	**<.01**	**0.44**	**<.001**	**0.63**	**<.001**
4th quartile stress	**0.39**	**<.001**	**0.85**	**<.001**	**1.11**	**<.001**
Stress (continuous)	**0.02**	**< .001**	**0.04**	**< .001**	**0.05**	**<.001**
Adjusted model *						
2nd quartile stress	0.14	.084	**0.25**	**<.05**	0.14	.473
3rd quartile stress	0.16	.054	**0.33**	**<.01**	0.28	.153
4th quartile stress	**0.23**	**<.05**	**0.50**	**<.001**	**0.46**	**<.05**
Stress (continuous)	**0.01**	**<.01**	**0.02**	**<.01**	0.01	.219

* Adjusted for sex, maternal education, low birth weight, pre-term birth, ethnicity, SES, teenage pregnancy, prenatal smoking and alcohol use, maternal and paternal history of depression, maternal prenatal depression, maternal prenatal anxiety, maternal postpartum depression, maternal stressful life events at 8 months, offspring stressful life events (at ages 1, 2, 3, 4, 5, and 6 years), and offspring symptoms of depression/anxiety at 81 months.

Table 4. Results of linear regression predicting child conduct disorder scores from quartile of maternal prenatal stress (regression coefficient, p value).

	7 years	9 years	11 years	13 years	16 years
Crude					
2nd Quartile	**0.15, p<.01**	**0.14, p<.01**	0.09, p=.093	**0.14, p<.01**	**0.11, p<.05**
3rd Quartile	**0.30, p<.001**	**0.23, p<.001**	**0.24, p<.001**	**0.25, p<.001**	**0.26, p<.001**
4th Quartile	**0.51, p<.001**	**0.43, p<.001**	**0.42, p<.001**	**0.51, p<.001**	**0.48, p<.001**
Stress (continuous)	**0.02, p<.001**	**0.02, p<.001**	**0.02, p<.001**	**0.03, p<.001**	**0.03, p<.001**
Adjusted*					
2nd Quartile	**0.10, p<.05**	0.08, p = .075	0.06, p=.176	**0.10, p<.05**	0.05, p=.333
3rd Quartile	**0.15, p<.01**	0.09, p = .069	**0.10, p<.05**	**0.10, p<.05**	**0.13, p<.05**
4th Quartile	**0.18, p<.001**	**0.13, p<.05**	**0.13, p <.05**	**0.18, p<.01**	**0.18, p<.01**
Stress (continuous)	**0.01, p<.05**	**0.01, p<.05**	**0.01, p<.01**	**0.01, p<.01**	**0.01, p<.01**

* Adjusted for sex, maternal education, low birth weight, pre-term birth, ethnicity, SES, teenage pregnancy, prenatal smoking and alcohol use, maternal and paternal history of depression, maternal prenatal depression, maternal prenatal anxiety, maternal postpartum depression, maternal stressful life events at 8 months, offspring stressful life events (at ages 1, 2, 3, 4, 5, and 6 years), and offspring symptoms of depression/anxiety at the same timepoint as the outcome.

Table 5. Results of linear regression predicting child hyperactivity scores from quartile of maternal prenatal stress (regression coefficient, p value).

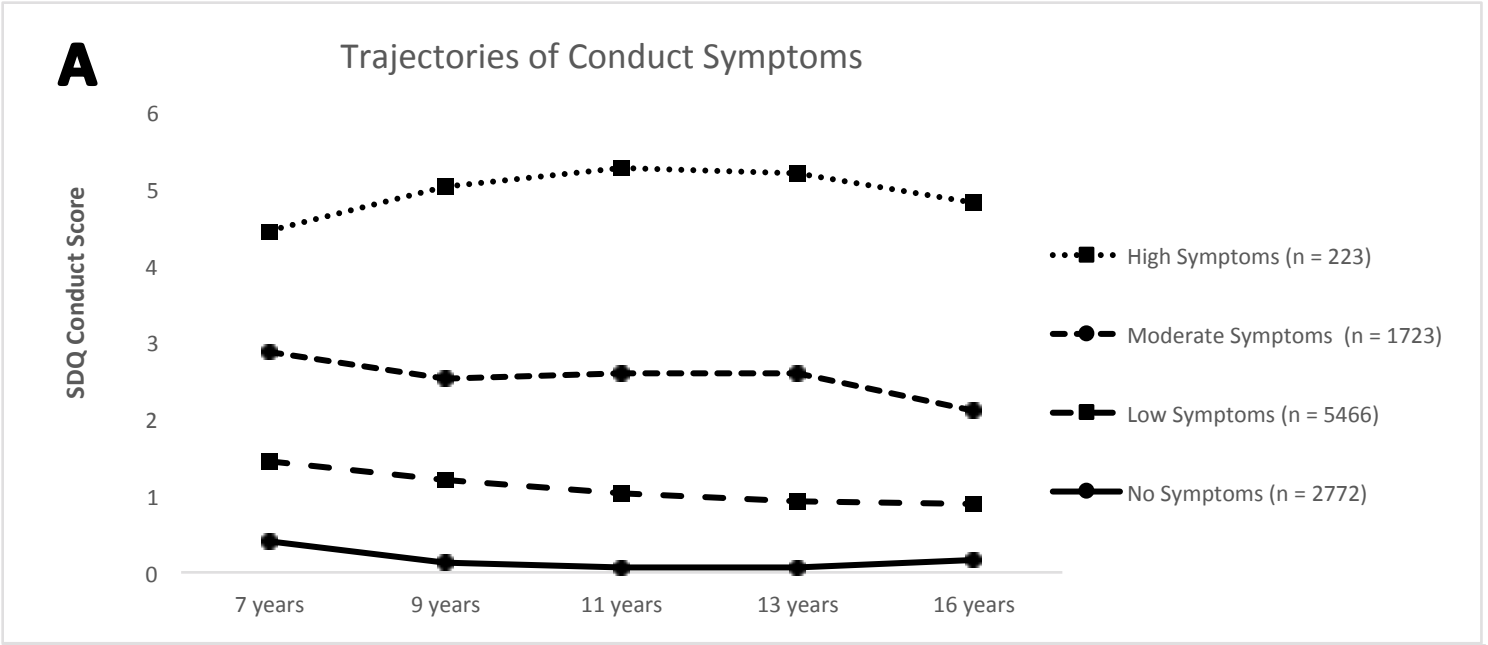
	7 years	9 years	11 years	13 years	16 years
Crude					
2nd Quartile	**0.25, p<.01**	**0.18, p<.05**	0.00, p=.987	0.08, p=.321	0.11, p=.192
3rd Quartile	**0.40, p<.001**	**0.312, p<.001**	**0.22, p<.05**	**0.29, p<.001**	**0.35, p<.001**
4th Quartile	**0.70, p<.001**	**0.65, p<.001**	**0.49, p<.001**	**0.64, p<.001**	**0.64, p<.001**
Stress (continuous)	**0.03, p<.001**	**0.03, p<.001**	**0.03, p<.001**	**0.04, p<.001**	**0.03, p<.001**
Adjusted*					
2nd Quartile	**0.20, p<.01**	0.12, p = .108	0.00, p=.999	0.04, p=.537	.043, p =.567
3rd Quartile	**0.22, p<.01**	0.12, p=.110	0.03, p=.717	0.11, p=.153	**0.15, p = .068**
4th Quartile	**0.31, p<.001**	**0.23, p < .01**	0.12, p=.153	**0.20, p<.05**	**0.19, p < .05**
Stress (continuous)	**0.01, p<.05**	0.01, p=.064	0.004, p=.282	**0.01, p<.01**	**0.01, p<.05**

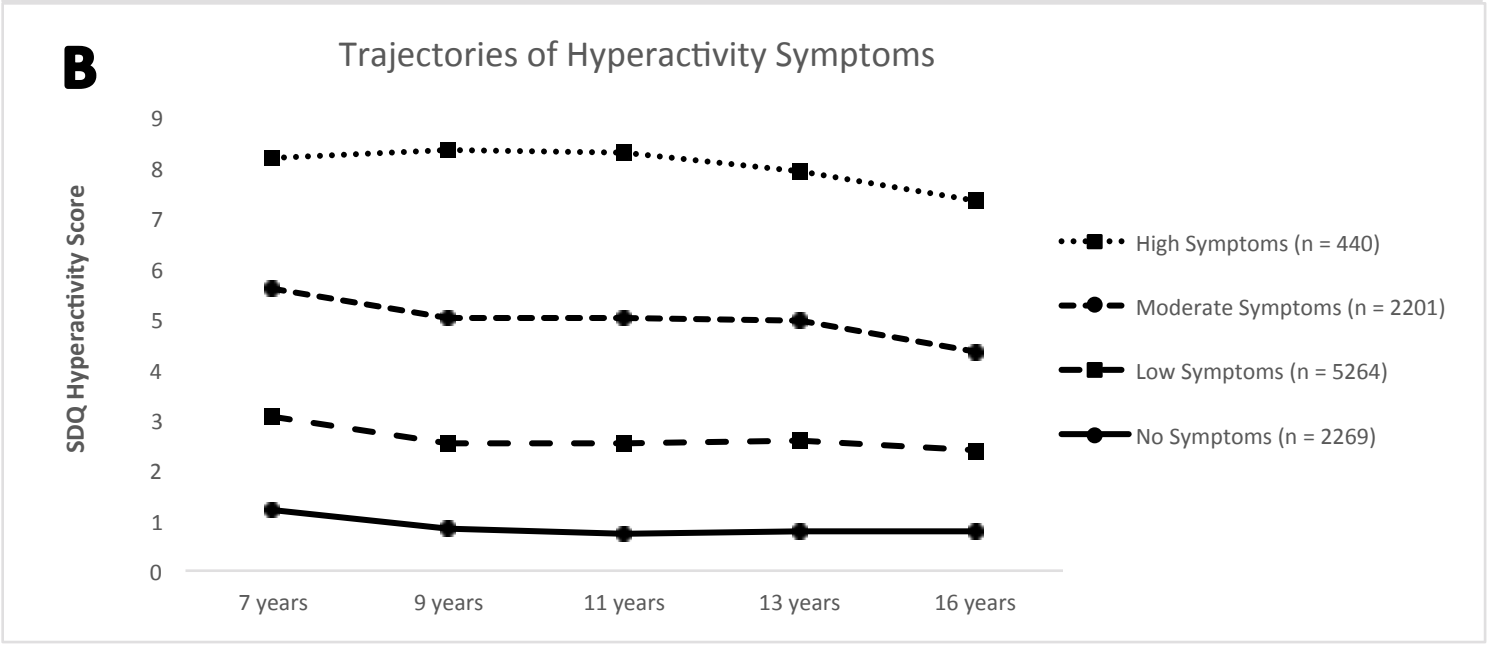
* Adjusted for sex, maternal education, low birth weight, pre-term birth, ethnicity, SES, teenage pregnancy, prenatal smoking and alcohol use, maternal and paternal history of depression, maternal prenatal depression, maternal prenatal anxiety, maternal postpartum depression, maternal stressful life events at 8 months, offspring stressful life events (at ages 1, 2, 3, 4, 5, and 6 years), and offspring symptoms of depression/anxiety at the same timepoint as the outcome.

FIGURE LEGENDS

Figure 1a: Trajectories of conduct disorder symptoms (n=10,184) over five time points in childhood/adolescence.

Figure 1b: Trajectories of hyperactivity symptoms (n=10,174) over five time points in childhood/adolescence.


A
Trajectories of Conduct Symptoms
SDQ Conduct Score
6
5
4
3
2
1
0
7 years
9 years
11 years
13 years
16 years
High Symptoms (n = 223)
Moderate Symptoms (n = 1723)
Low Symptoms (n = 5466)
No Symptoms (n = 2772)


B
Trajectories of Hyperactivity Symptoms
SDQ Hyperactivity Score
9
8
7
6
5
4
3
2
1
0
7 years
9 years
11 years
13 years
16 years
High Symptoms (n = 440)
Moderate Symptoms (n = 2201)
Low Symptoms (n = 5264)
No Symptoms (n = 2269)

Supplemental Table 1: Results of attrition analyses

	With complete outcome data	**Missing outcome data at age 16**		
	% of sample		**χ^2**	**p-value**
Sex (Male)	49.47	54.86	21.60	< 0.001
Preterm Birth	4.99	5.44	0.78	0.376
Low Birth weight	4.27	4.53	0.29	0.592
Teen Pregnancy	0.94	3.61	66.95	< 0.001
Maternal smoking, last 2 weeks	11.27	21.00	135.79	< 0.001
Maternal alcohol misuse, first trimester	15.76	15.18	0.48	0.489
Low maternal Education	48.38	29.41	269.44	< 0.001
Non-white Child Ethnicity	3.18	4.33	6.68	< 0.05
Low SES (Non-professional)	2.58	6.01	52.72	< 0.001
Mother ever depressed	6.10	9.80	35.55	< 0.001
Maternal prenatal depression	8.99	13.37	36.92	< 0.001
Maternal prenatal anxiety	10.63	14.36	24.15	< 0.001
Maternal postnatal depression	6.35	8.82	7.34	< 0.001
Partner ever depressed	4.93	6.62	7.02	< 0.01
	Mean (SD)		**t**	**p-value**
Maternal postnatal stress	9.41 (7.60)	9.69 (8.16)	-1.50	0.133
Child SLES age 1	0.92 (1.07)	0.95 (1.06)	-0.84	0.397
Child SLES age 2	1.36 (1.23)	1.33 (1.30)	1.01	0.308
Child SLEs age 3	1.63 (1.23)	1.60 (1.30)	0.94	0.347
Child SLES age 4	2.30 (1.34)	2.36 (1.44)	-1.76	0.077
Child SLES age 5	1.40 (1.23)	1.44 (1.30)	-1.36	0.173
Child SLES age 6	1.36 (1.41)	1.50 (1.52)	-4.01	< 0.001
Maternal prenatal stress	7.79 (6.91)	8.55 (7.74)	-4.51	< 0.001
Conduct score at age 16	1.51 (1.42)	1.73 (1.52)	-6.44	< 0.001
Hyperactivity score at age 16	3.24 (2.31)	3.57 (2.42)	-5.98	< 0.001

Supplemental Table 2: Percentage prevalence of independent stressful life events occurring since pregnancy in the study sample.

Stressful Life Event	**Prevalence (n=15415)**
Your partner died	**0.1**
One of your children died	0.1
A friend or relative died	10.1
One of your children was ill	12.8
Your partner was ill	9.9
A friend or relative was ill	14.9
You were admitted to hospital	2.9
You were in trouble with the law	0.6
You were divorced	0.8
You found out that your partner didn't want your child	2.5
You were very ill	7.1
Your partner lost his job	5.1
Your partner had problems at work	15.8
You had problems at work	11.2
You lost your job	2.8
Your partner went away	6.4
Your partner was in trouble with the law	2.0
You and your partner separated	3.0
Your income was reduced	16.2
You argued with your partner	29.3
You had arguments with your family or friends	14.0
You moved house	8.0
Your partner hurt you physically	1.3
You became homeless	1.1
You had major financial problems	10.7
You got married	2.6
Your partner hurt your children physically	0.1
You attempted suicide	0.1
You were convicted of an offence	0.2
You were bleeding and thought you might miscarry	13.0
You started a new job	3.7
You had a test to see if your baby was abnormal	41.6
You had a result on a test that suggested your baby might not be normal	3.0
You were told you were going to have twins	2.7
You heard that something that had happened might be harmful to the baby	6.7
You tried to have an abortion	0.7
You took an examination	4.5
Your partner was emotionally cruel to you	4.7
Your partner was emotionally cruel to your children	0.5
Your house or car was burgled	4.1
You had an accident	3.0
Other	9.2

Supplemental Table 3: Comparison of model parameters for two-, three-, four-, five- and six-group trajectory models.

PP = Posterior Probability

(A) Trajectories of conduct disorder symptoms

Model	BIC	PP group 1	PP group 2	PP group 3	PP group 4	PP group 5	PP group 6
1-Group	-60631.24						
2-Group	-56987.9	88.81%	87.74%				
3-Group	-55654	86.55%	86.63%	85.22%			
4-Group	-55380.32	82.85%	82.12%	77.39%	85.37%		
5-Group	-55191.22	75.25%	68.38%	81.75%	76.84%	84.41%	
6-Group	-55044.29	65.95%	69.54%	72.08%	74.92%	79.24%	87.55%

(B) Trajectories of hyperactivity symptoms

Model	BIC	PP group 1	PP group 2	PP group 3	PP group 4	PP group 5	PP group 6
1-Group	-79765.57						
2-Group	-74492.82	93.39%	89.42%				
3-Group	-72445.35	86.91%	86.08%	89.79%			
4-Group	-71688.74	85.43%	82.69%	84.17%	89.23%		
5-Group	-71311.97	80.92%	79.44%	77.84%	79.87%	86.69%	
6-Group	-71214.81	80.74	66.63%	78.52%	68.80%	80.27%	87.10%

Supplemental Figure 1: Study sample inclusion criteria for conduct disorder (A) and hyperactivity (B)